Dry Water for Future Inhaled Medicines

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Background

- Dry water (DW) is the stable dispersion of water in air. It is a are free–flowing dry powders that contain approximately 98% water.[1]
- DW is a method of coating water droplets with hydrophobic fumed silica particles to appear as a flowable powder, but it contains larger amounts of biologics trapped inside.[11]
- DW allows for the creation of unstable biological formulations, such as aerosols, which enhance thermostability, aerosol properties, and flexibility of administration. This could improve safety and efficacy and be beneficial for biological therapies. [2]
- Dry powder formulations, while freeing protein molecules from mechanical stress during aerosolization, may be unstable and more prone to degradation. DW formulations overcomes the issues of degradation in the dry powder state.[3]
- The drug delivery system involves the active release of a drug to achieve a desired therapeutic response. Upper airways deposit particle sizes 10 μm, the conducting airways deposit particle sizes 5 μm and respiratory airways deposit particle sizes 2 μm.[4]

1.Wang H, Fu Z, Ji X, Lu M, Deng L, Liu Z, et al. A general method for endowing hydrophobic nanoparticles with water dispersion abilities. Journal of Materials Chemistry B. 2023;11(35):8464-70. 2.Chhabra N, Arora M, Garg D, Samota MK. Spray freeze drying-A synergistic drying technology and its applications in the food industry to preserve bioactive compounds. Food Control. 2023:110099. 3. Williams III R. Improved Formulations to Enable Stable Delivery of Biologics. BioPharm International. 2022;35(7):46-9--9. 4.Ezike TC, Okpala US, Onoja UL, Nwike PC, Ezeako EC, Okpara JO, et al. Advances in drug delivery systems, challenges and future directions. Heliyon. 2023.

Research Hypothesis and Objectives

DW is the stable dispersion of water in air. It proposes significant advantages in drug delivery as we can use DW to formulate biologics for drug delivery and delivering biologics such as proteins, which cannot be stabilised without water.

However, the formulation of stable powders of DW to the airways, which maintain sensitive therapeutic proteins in their native structure, remains unknown. Therefore, we hypothesise that if we can produce DW particles with an acceptable excipient toxicity profile, this would enhance aerosol drug delivery of challenging biological molecules.

This project aims to explore DW formulations for delivery to the airways by employing *in vitro* lung toxicology models to examine the toxicity and potential safety of hydrophobic silica colloids required for DW formulation. Furthermore, it will establish DW particle manufacturing approaches that prepare DW particles with appropriate physicochemical properties for aerosol drug delivery. Once the DW formulation has been established, we will examine the loading and liberation processes for DW particles and understand the particle structure and its impact on DW particle behaviour. Finally, we aim to examine the application of DW particle medicines in aerosol drug delivery.

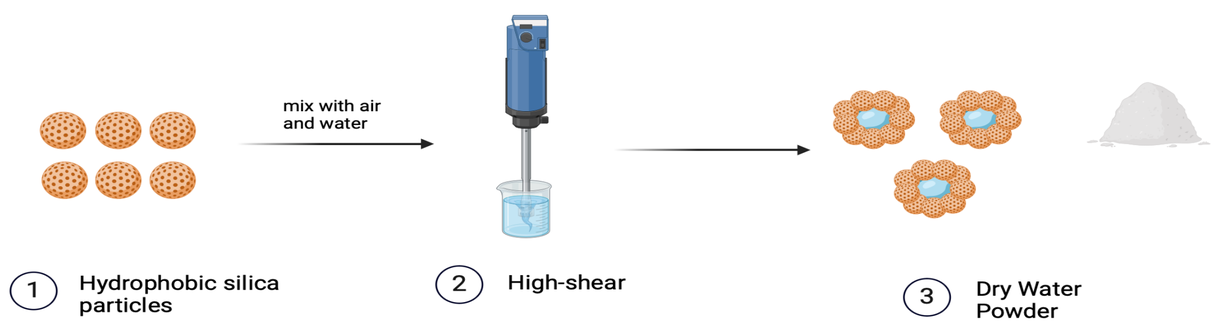

Figure 2. Mechanism of DW Formulations.[11]

11.Saleh K, Forny L, Guigon P, Pezron I. Dry water: From physico-chemical aspects to process-related parameters. Chemical engineering research and design. 2011;89(5):537-44.

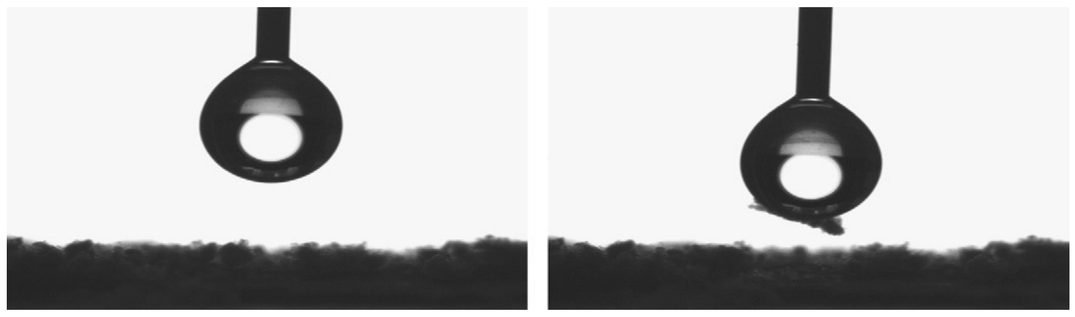

Figure 1. Macroscopic demonstration of adhesion of hydrophobic particles.[11]

11.Saleh K, Forny L, Guigon P, Pezron I. Dry water: From physico-chemical aspects to process-related parameters. Chemical engineering research and design. 2011;89(5):537-44.

Programme and Methodology

DW excipient toxicity

- Toxicology assays determine the toxicology of excipient substances and formulations during processing, actuation, and liberation.
- MTT assays, which measure cell viability, cytotoxicity, and proliferation.
  - LDH assay can detect cytotoxicity in alveolar epithelium cells.

DW manufacturing

- Aggregation of nanoparticles can significantly impact the size of DW formulations.
- Small-angle neutron scattering (SANS) aids in studying multicomponent complex structure through contrast variation and deuterium labelling.
- Laser scattering accurately determines the size of DW in various materials like liquids, solids, and aerosols.

Aerosolization of drug delivery

- DW would have a carrier–based formulation that will help improve DW flow properties. It will look at blends between silica particles and medications in order to aid dispersion.
- Next Generation Impactors (NGI) has seven stages and controls at any inlet flow rate between 30–100 L/min and a cut size ranging from 0.54 – 11.7 μm D_A at 30 L/min and 0.24 – 6.12 μm at 100 L/min.
- DW particle separation and sizing are achieved by increasing the velocity of the airstream as it passes through each stage by forcing it through a series of nozzles containing progressively reducing jet diameters

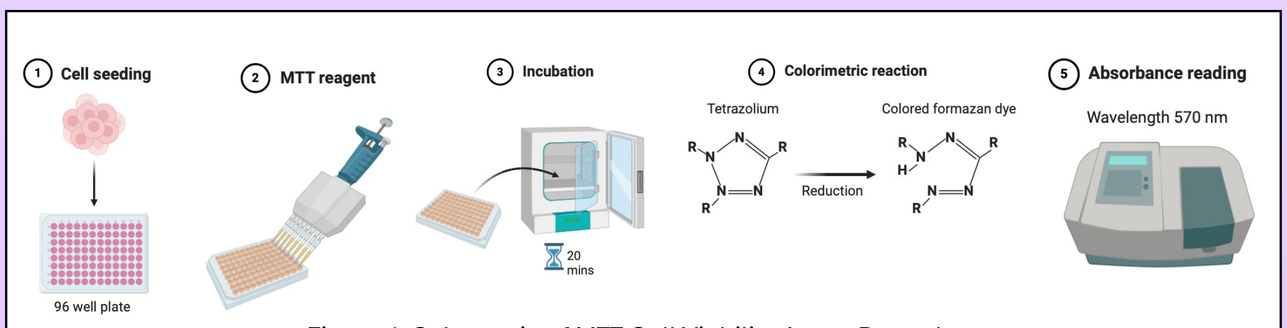

Figure 4. Schematic of MTT Cell Viability Assay Procedure

Responsible Innovation

DW, a novel pharmaceutical concept, requires accurate information and marketing to increase public awareness and receptiveness to its use in future inhaled medicines, enhancing effective healthcare.[5]

We still do not know if we can stabilize biologics that cannot be stabilized without water and can contain sensitive therapeutic proteins. However, DW formulation poses risks as bacteria or viruses can maintain their biological states.[6]

Transparency in new medicine development enhances drug access, promotes ethical practices, and increases trust, facilitating better decision-making and policymaking.[7]

Financial barrier to access for low-middle-income countries (LMIC), as the high costs make medication unaffordable.[8]

5.Smolynets I, Gutyj B, Petryshak O, Lytvyn R. Pharmaceutical marketing: objectives and types. Науковий вісник Львівського національного університету ветеринарної медицини та біотехнологій імені С3 Ґжицького. 2016;18(2-4 (69)):151-4. 6.Tin D, Sabeti P, Ciottone GR. Bioterrorism: an analysis of biological agents used in terrorist events. The American Journal of Emergency Medicine. 2022;54:117-21. 7.Esfandiari A, Yazdi-Feyzabadi V, Zarei L, Rashidian A, Salari H. Transparency in public pharmaceutical sector: the key informants' perceptions from a developing country. BMC Health Serv Res. 2021;21(1):1316. 8.Leisinger KM, Garabedian LF, Wagner AK. Improving access to medicines in low and middle income countries: corporate responsibilities in context. Southern med review. 2012;5(2):3.

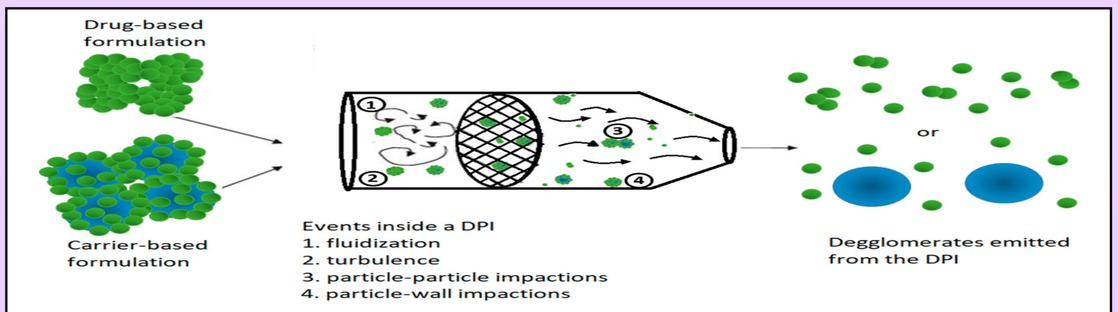

Figure 3. Schematic of DPI dispersion mechanism.[12]

12.Zheng Z, Leung SSY, Gupta R. Flow and particle modelling of dry powder inhalers: Methodologies, recent development and emerging applications. Pharmaceutics. 2021;13(2):189.

Scientific Innovation

DW is an innovative inhaled formulation for future biologics, enhancing patient adherence, as most biologics are delivered parenterally, with some exceptions being ocular or inhaled formulations. DW application aims to reduce incorrect inhaler usage and the need for trained professionals, enabling less trained professionals like teachers to administer drugs and use the application more efficiently.

DW application improves sterility and cost-effectiveness for LMICs by allowing storage in cool, dry places, reducing constant sterile conditions and improving inventory management, thereby enhancing patient care. DW increases access to medicines for low-income individuals by providing stable biologics and making them more cost-efficient, improving their quality of life and accessibility to DW applications.

9.Zhang C, D'Angelo D, Buttini F, Yang M. Long-acting inhaled medicines: Present and future. Advanced Drug Delivery Reviews. 2023:115146.
10.Yenet A, Nibret G, Tegegne BA. Challenges to the Availability and Affordability of Essential Medicines in African Countries: A Scoping Review. ClinicoEconomics and Outcomes Research. 2023:443-58.

Statement of the problem

Pulmonary toxicology of inhalable microparticle–based DW may be problematic in DW formulation as it consists of hydrophobic fumed silica particles. DW contains nanoparticles, it is unknown what impact this would have on pulmonary toxicity since they are formulated into microparticles.

Controlled drug release is important when it comes to DW; however, we are uncertain how the properties of the nanoparticles necessary to prepare DW particles impact the drug release rates and the potential control release.

To aerosolize DW formulation, it is important to consider designing it as micron–sized particles encapsulating or aggregated nanoparticles. Several challenges have arisen since DW has never been evaluated for respiratory drug delivery. Many DW formulations for inhaled therapy will be modelled with current dry powder inhaled therapy.

Challenges

Challenging areas of the proposed reach: DW formulation and device design application

- How can we prepare DW of the right particle size for this application?
- What particle size do we need for which application? Do we know from the literature that we can make DW particles in that range?
- What are the best devices to allow effective administration?
- How can the biologic be liberated from the DW after administration?
- Toxicology effects of the colloidal excipient